Longitudinal Changes in Autosomal Dominant AD

John C. Morris, MD

Harvey A. and Dorismae Hacker Friedman
Distinguished Professor of Neurology

Washington University in St. Louis
School of Medicine

DIAN
Dominantly Inherited Alzheimer Network

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

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(with gratitude to our participants and families!)

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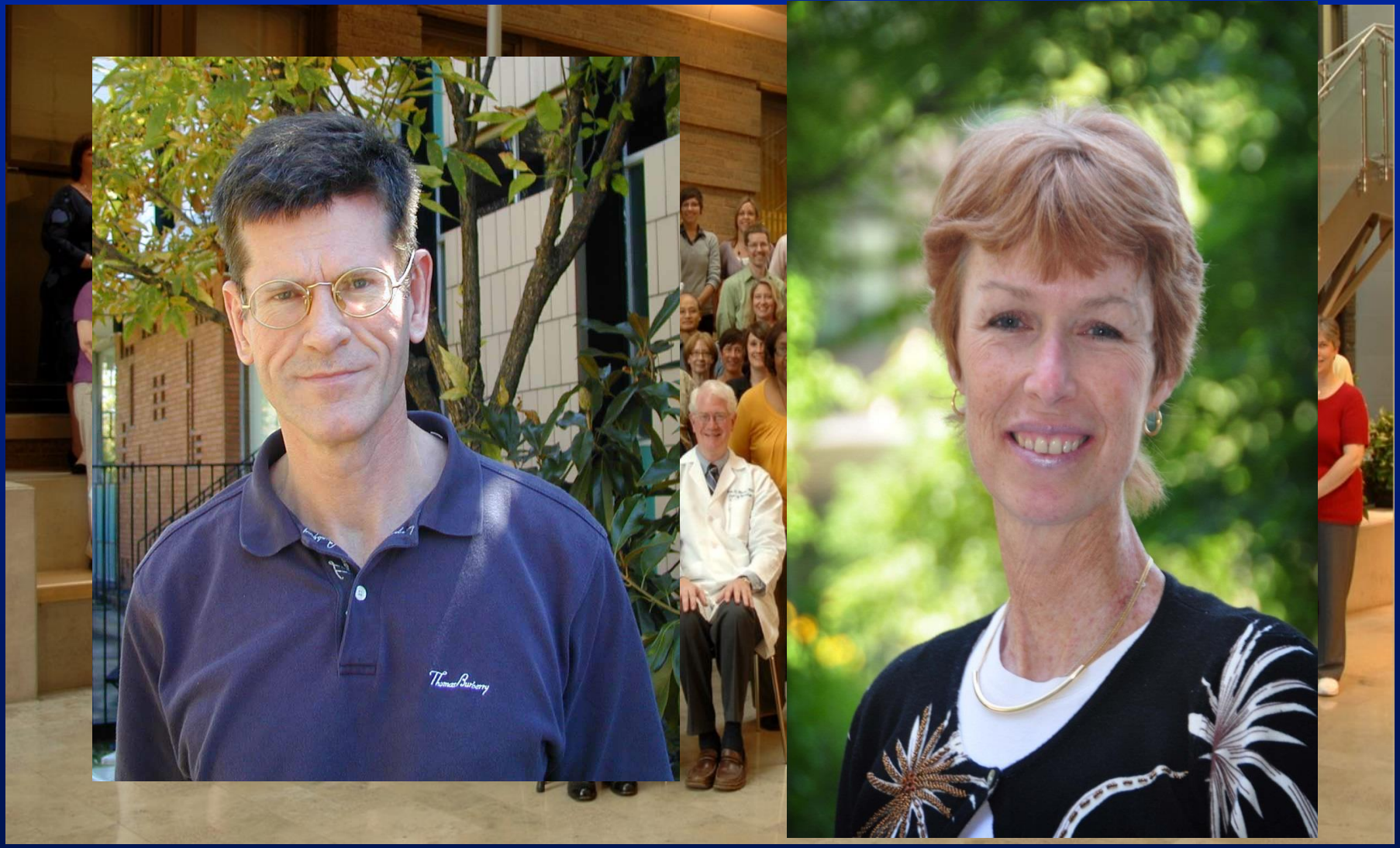

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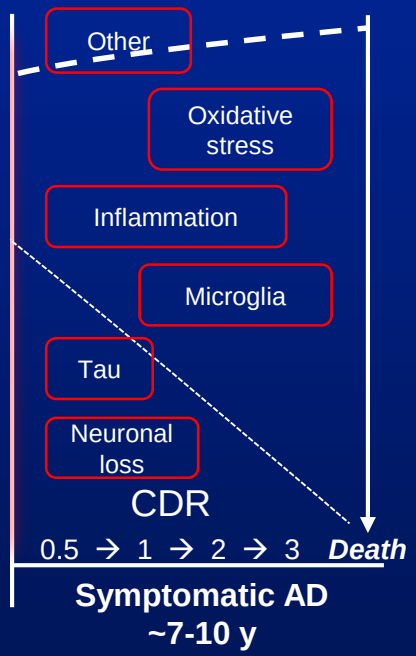
Preclinical and Symptomatic AD

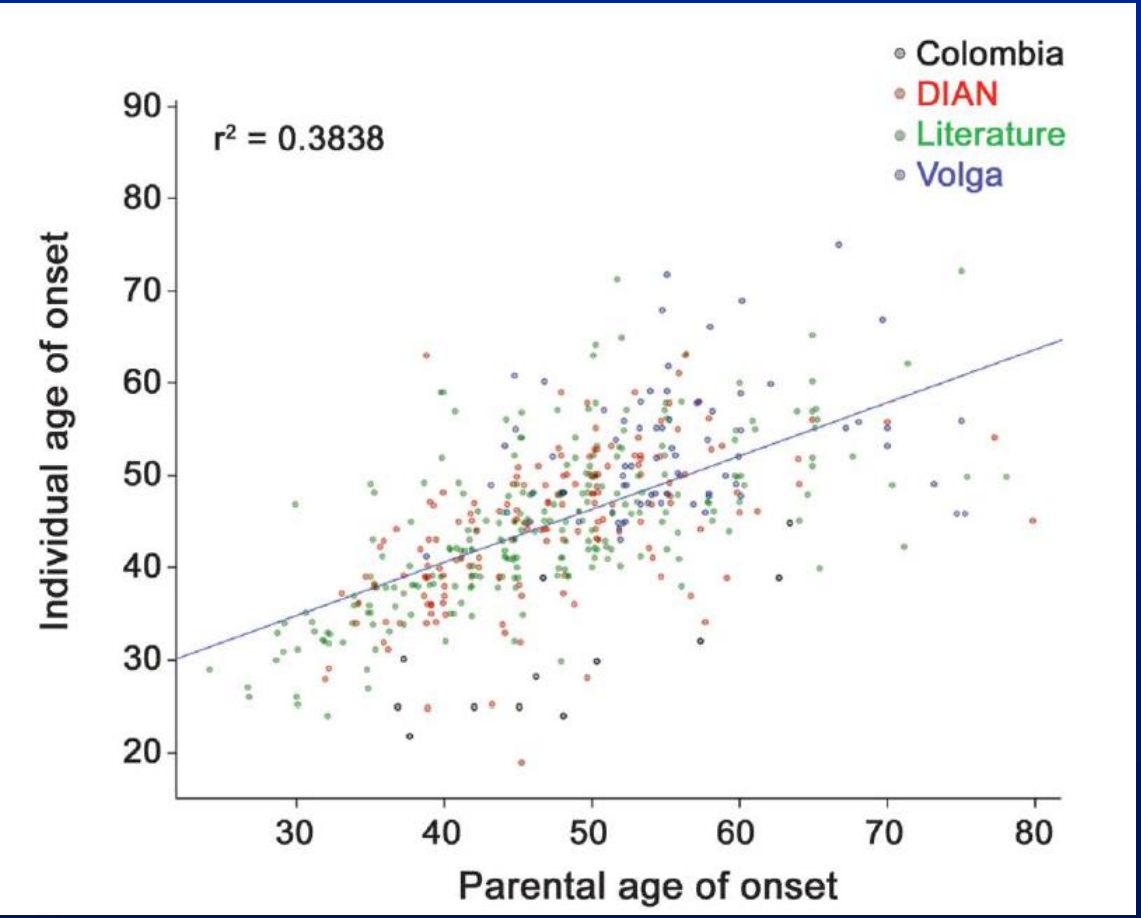


Preclinical Alzheimer Disease

- ~30% of cognitively normal older adults have biomarker evidence of preclinical AD
- Biomarker-positive CN persons are at increased risk of developing symptomatic AD compared with biomarker-negative CN older adults
- However, individual level prediction not currently possible
  - Is symptomatic AD inevitable?
  - If so, when will it develop?
- Asymptomatic AD mutation carriers are destined to develop symptomatic AD, and at about the same age as their affected parent

Predictable Age of Onset in ADAD –

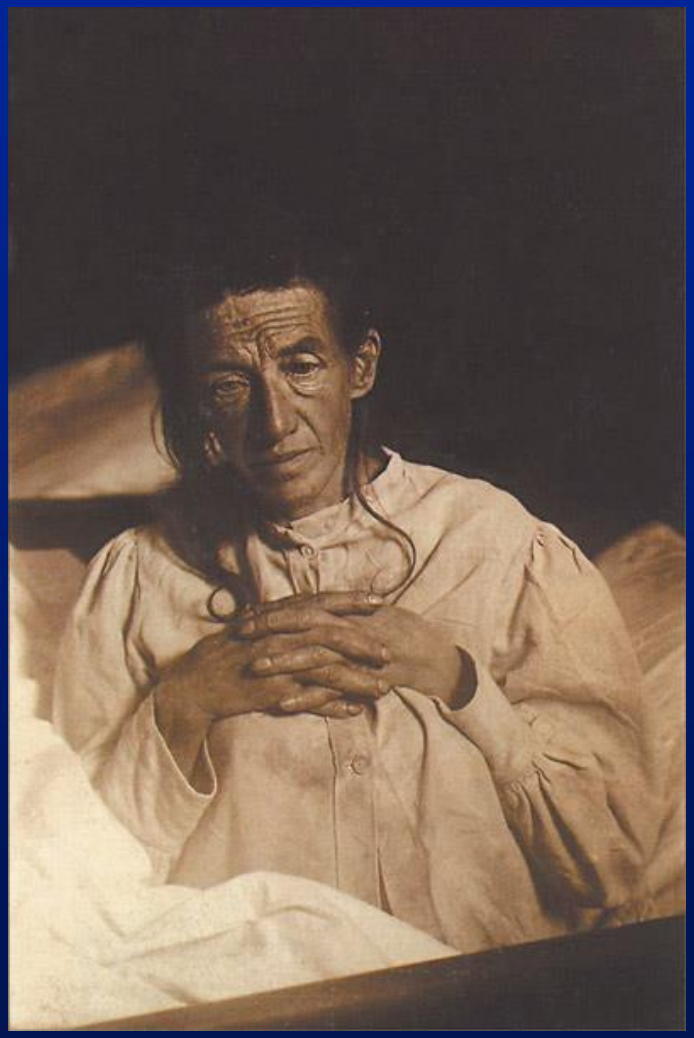
- Autosomal dominant mutations are ~100% penetrant



Ryman et al., Neurology 2014

Autosomal Dominant Alzheimer's Disease (ADAD)

- <1% of AD cases have mutations in 3 genes directly involved in amyloid beta (Aβ) production: *APP*, *PSEN1*, *PSEN2*
- Auguste D., the first AD patient, had an ADAD mutation in *PSEN1* (F176L): Muller et al., 2013; Lancet Neurol 12:129-130
- 21 yrs from pathogenic (*APP*; Goate et al., 1991; Nature 349: 704-706) to protective (*APP A673T*; Jonsson et al., 2012; Nature 488: 96-99) mutations



DIAN Aims

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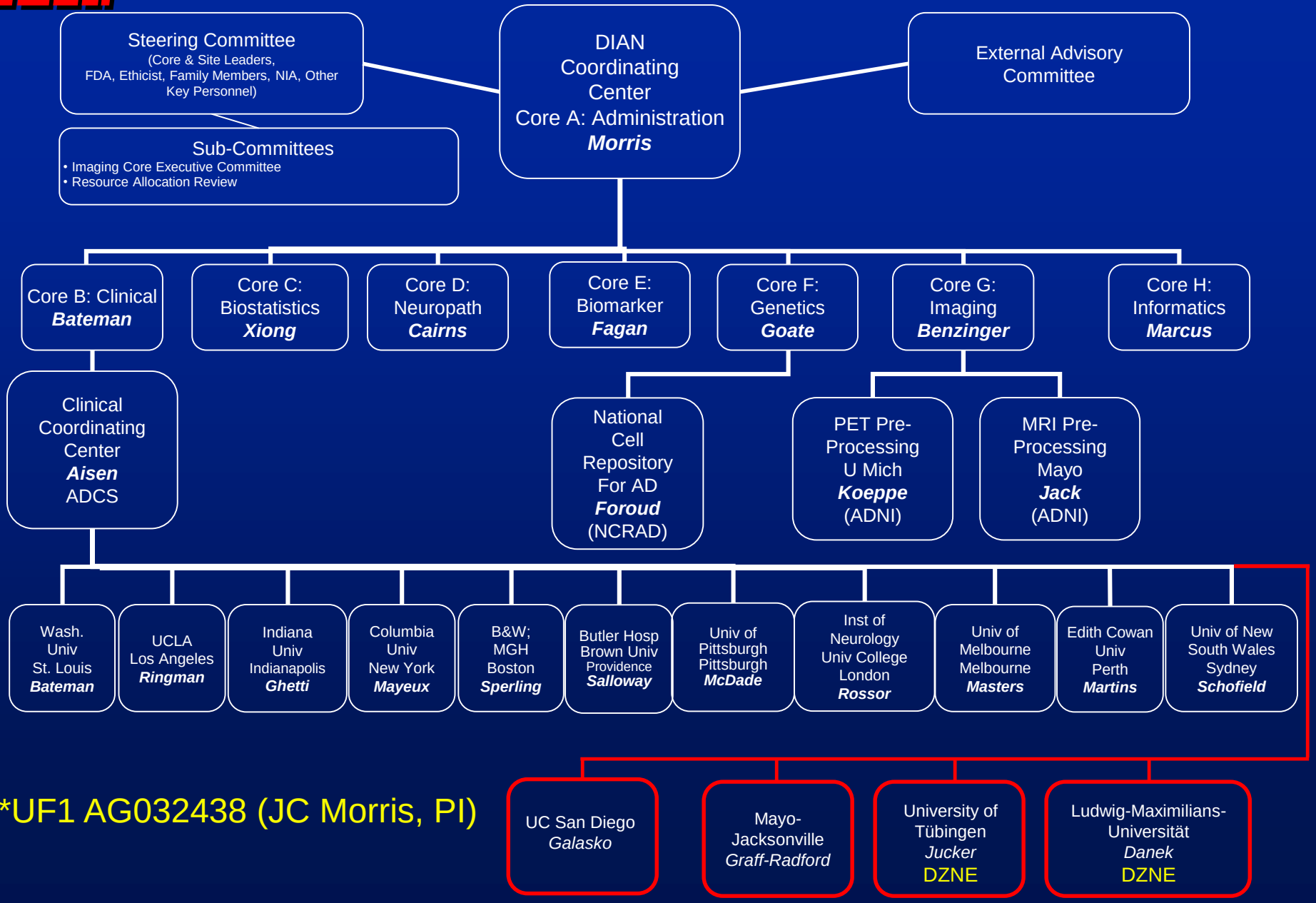
Dominantly Inherited Alzheimer Network

- Determine WHEN the pathobiology of AD begins in asymptomatic mutation carriers (MCs) in relation to parental age of onset of dementia
- Determine the SEQUENCE and RATE of the pathobiological changes
- Compare the clinical and pathological phenotypes of dominantly inherited AD with late onset AD
- Establish an international, longitudinal registry of 400 persons (~200 MCs, ~200 NCs) from families with a known pathogenic mutation for AD

Dominantly Inherited Alzheimer Network (DIAN)*



*UF1 AG032438 (JC Morris, PI)

Participant Entry Characteristics

Total N = 409* *(*Table based on **386** participants; **23** mutations are in process)*	**Asymptomatic** 296 (72.4%)		**Symptomatic** 113 (27.6%)	
	MUT: 274 (71.0%)		MUT: 112 (29.0%)	
	131 (NC-)	143 (MC+)	12 (NC-)	100 (MC+)
Age	38.3 (SD 10.0)	34.8 (SD 9.0)	40.8 (SD 11.6)	45.5 (SD 10.2)
Gender (% Female)	56.5%	57.3%	66.7%	56.0%
Parental Age of Onset	46.68 (SD 6.8)	47.4 (SD 7.2)	46.5 (SD 6.4)	45.9 (SD 8.4)
Education	14.9 (SD 2.6)	14.4 (SD 2.9)	12.1 (SD 4.1)	13.2 (SD 3.1)
MMSE	29.2 (SD 1.2)	29.0 (SD 1.2)	28.1 (SD 1.6)	22.4 (SD 7.1)
ApoE4+ ***1 E4***	38	34	1	25
2 E4	1	2	0	5

MC = Mutation Carrier; NC = Non-carrier

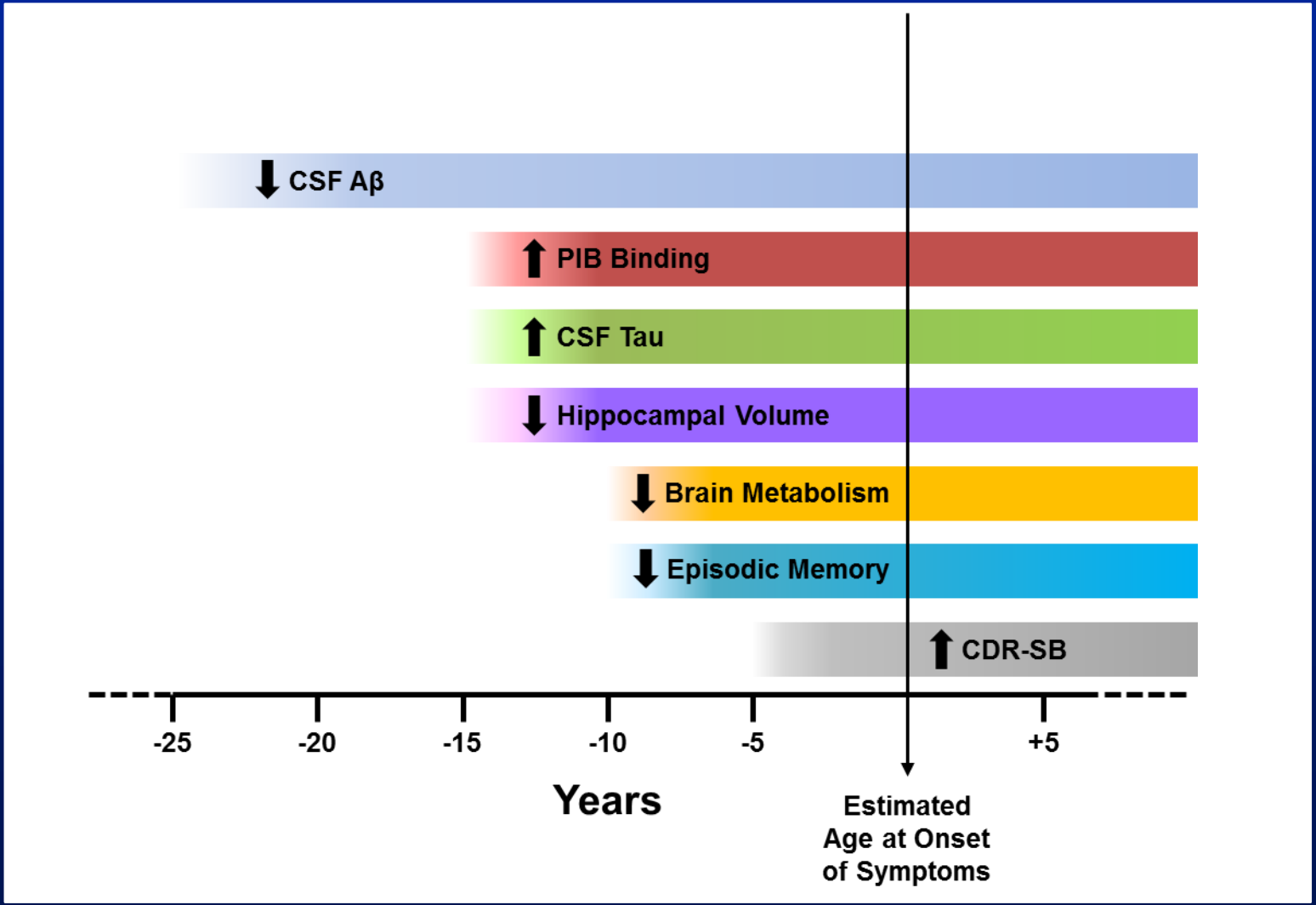
*Table statistics based on 386 participants with NCRAD-confirmed mutation data available as of 30 SEP 2014

Procedure Completion Rates (as of September 30, 2014)

Procedure	Baseline N= 409	In Person Follow-up N= 248
Cognitive battery		
-UDS	99%	96%
-Computerized	93%	85%
Nonfasted Blood (for genetics)	100%	N/A
Fasted blood	97%	99%
MRI	94%	90%
PET PIB	87%	83%
FDG PET	88%	86%
Lumbar Puncture	80%	71%

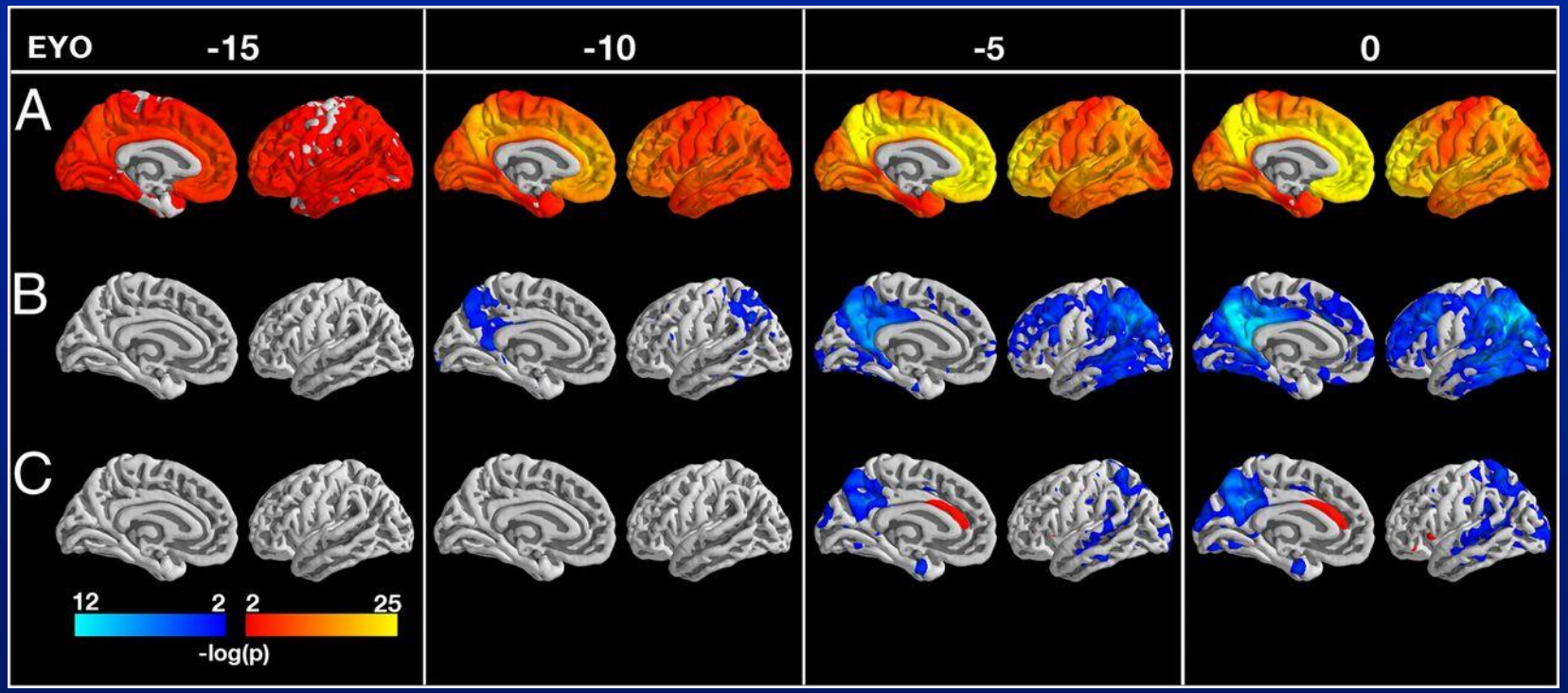
Missed F/U rate = 11%

Alzheimer Biomarker Pathochronology in Autosomal Dominant AD



Morris et al., Clin Invest 2012

Amyloid, FDG and Atrophy



PiB

FDG

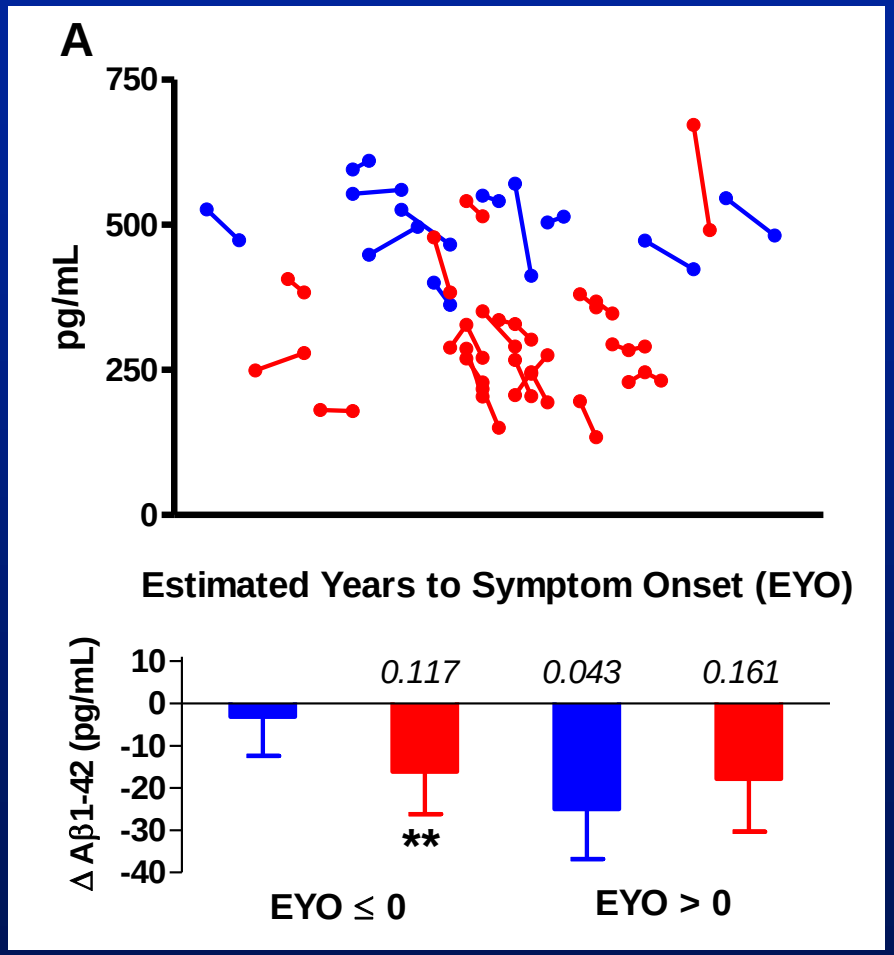
Atrophy

- Statistical significance (P value) maps on medial and lateral left cortical gray surface showing differences between carriers and noncarriers in PiB (A), FDG (B), and cortical thickness (C) at −15, −10, −5, and 0 y before predicted symptom onset

[DF4, n=229]

Benzinger, Blazey et al. PNAS 2013

Within-person Longitudinal Change in CSF Aβ42 as a Function of EYO



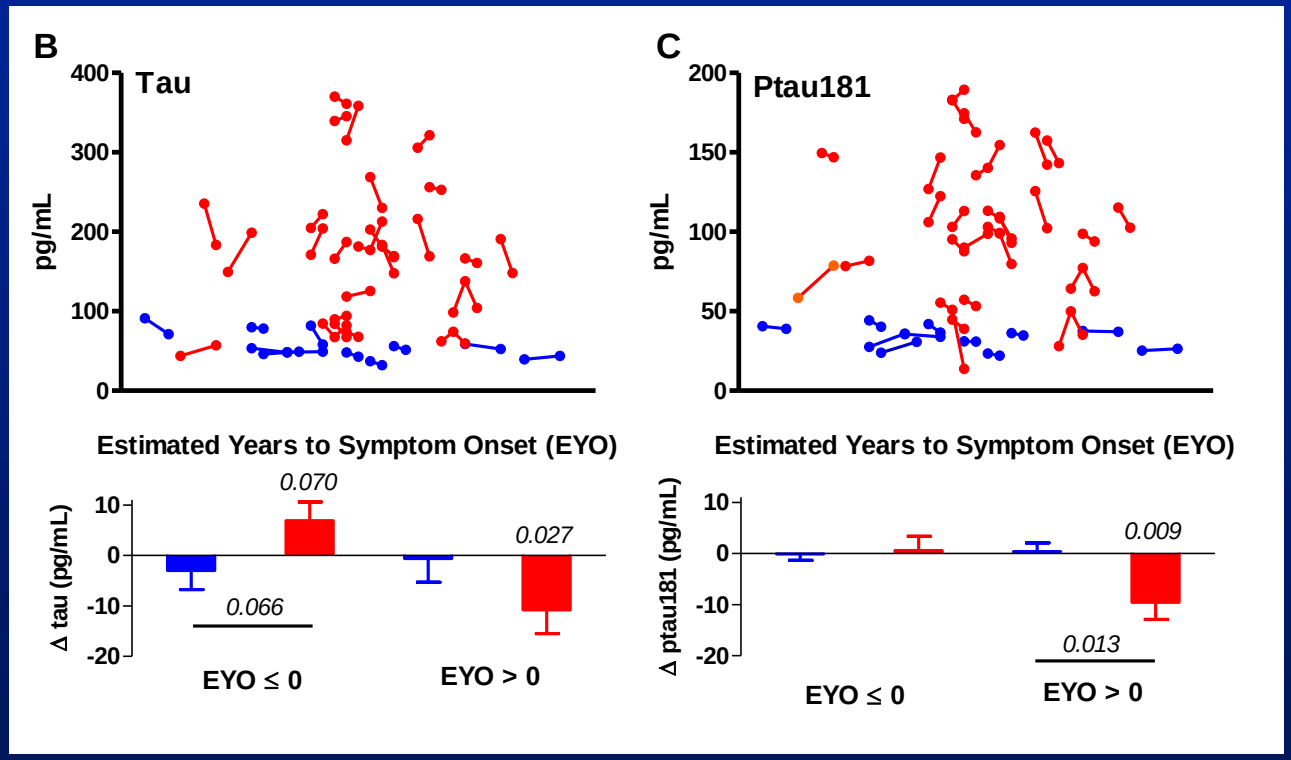
- **N=11 NC**
- **N=26 MC**
  - N=9 MC-AS
  - N=17 MC-S

Longitudinal samples run on the same assay plate

P values comparing the slopes to zero

(Fagan et al., 2014, Sci Transl Med)

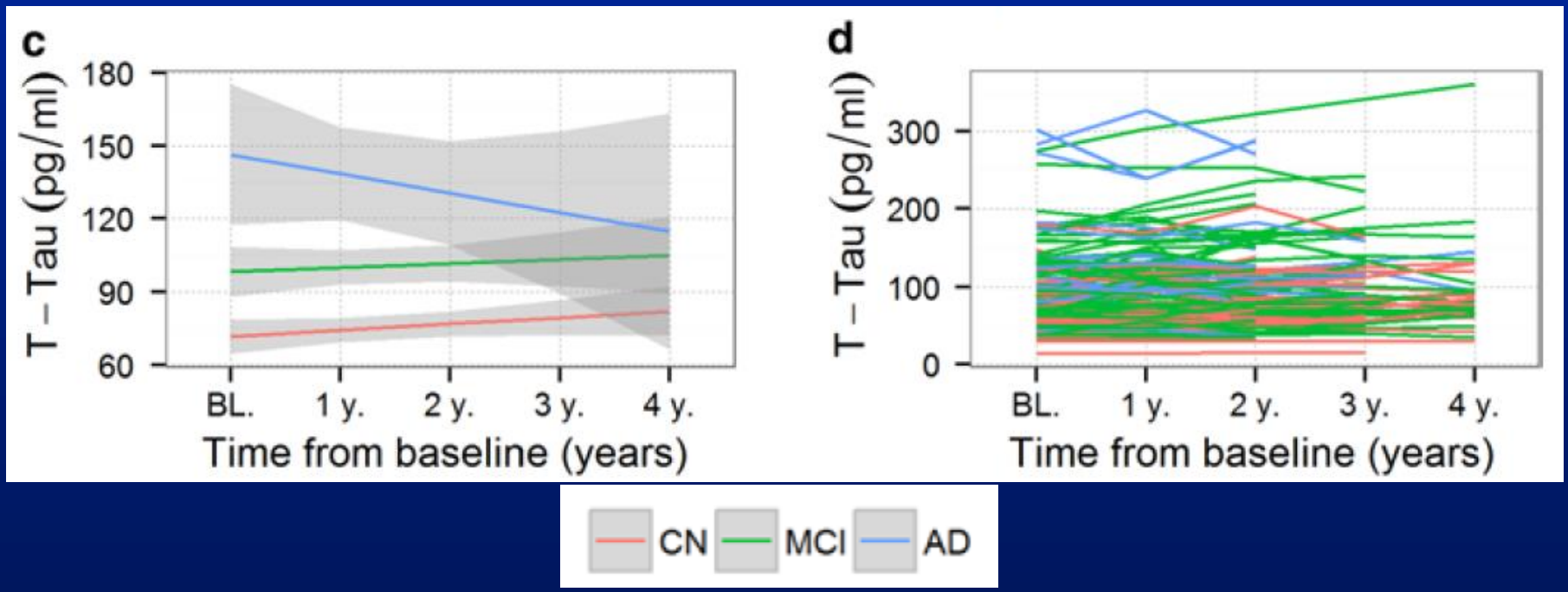
Within-person Longitudinal Change in CSF Neuronal Injury Markers as a Function of EYO



- **N=11 NC**
- **N=26 MC**
  - N=9 MC-AS
  - N=17 MC-S

(Fagan et al, 2014, Sci Transl Med)

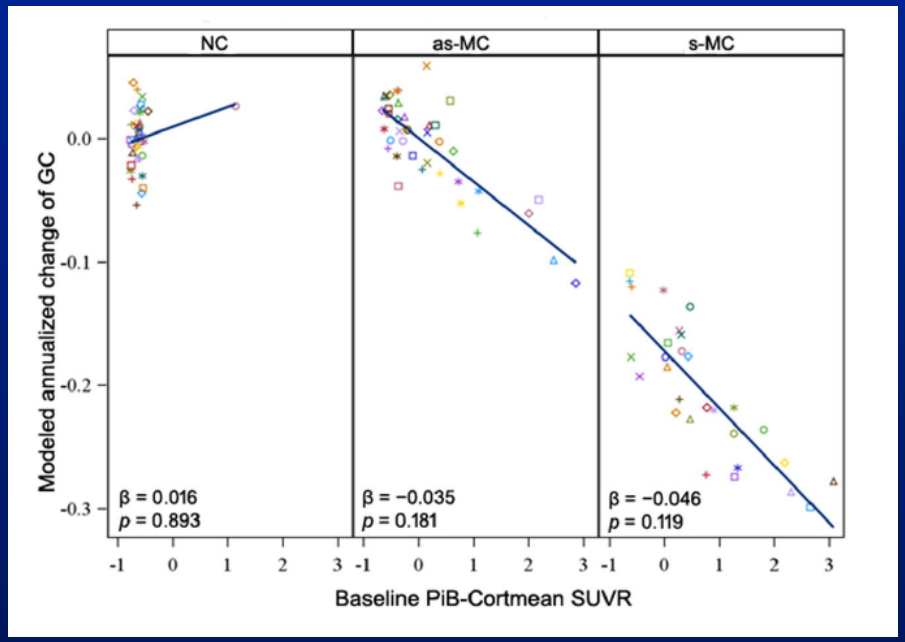
Reductions in CSF Tau in ADNI Participants with Symptomatic AD



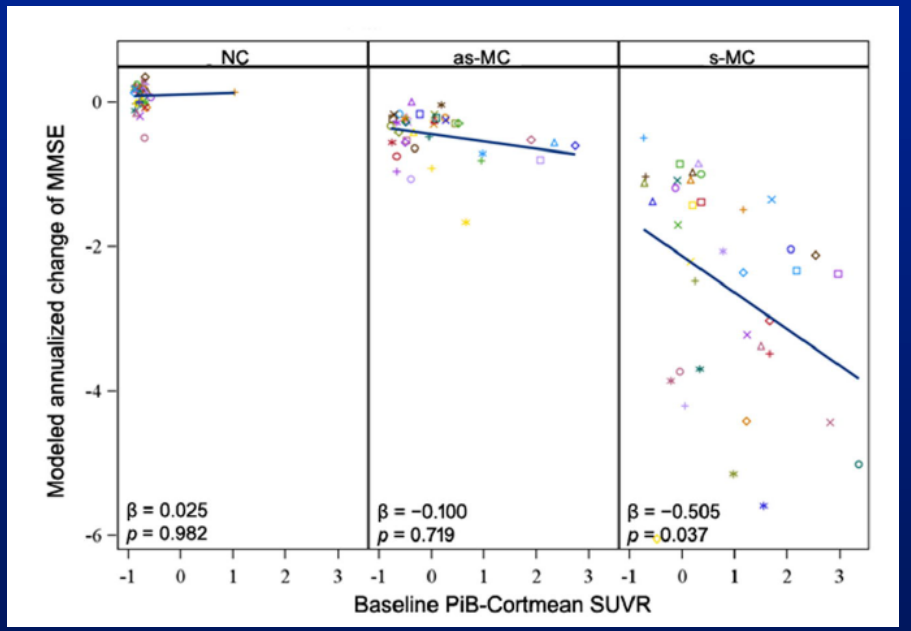
(Toledo et al., 2013, Acta Neuropathol)

Cognitive Decline Over Time as Predicted by Baseline PIB-PET

Global Composite



MMSE

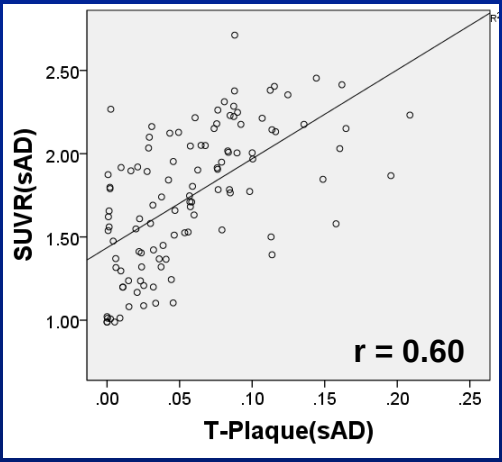


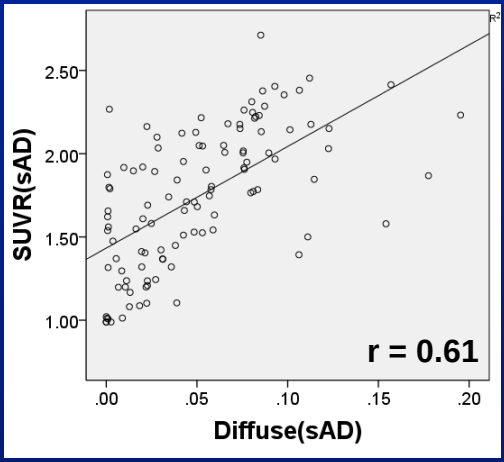
<Confidential>

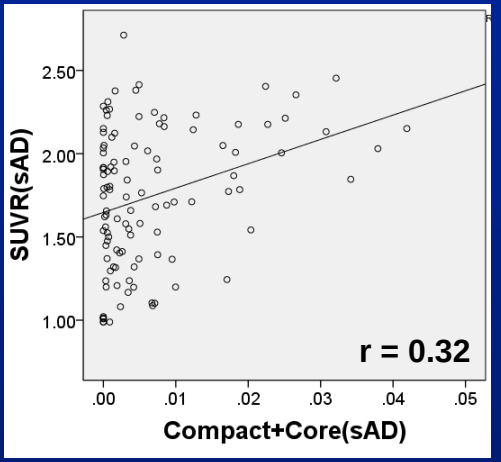
Fen Wang and Brian Gordon, unpublished

Correlation Between PiB-PET and Postmortem Plaques in Sporadic AD (N=7) and ADAD (N=7) Cases

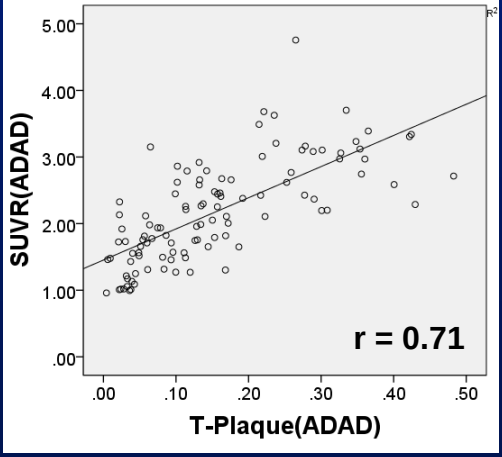
Sporadic AD

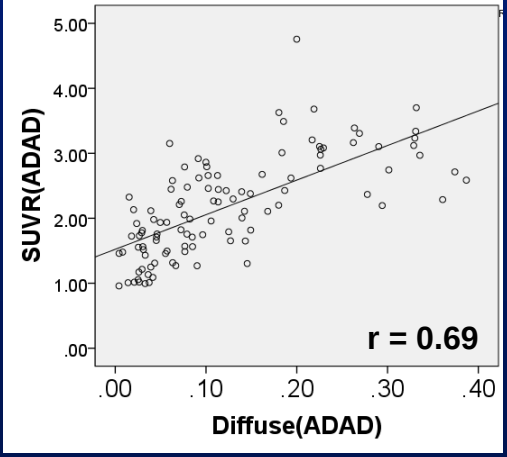


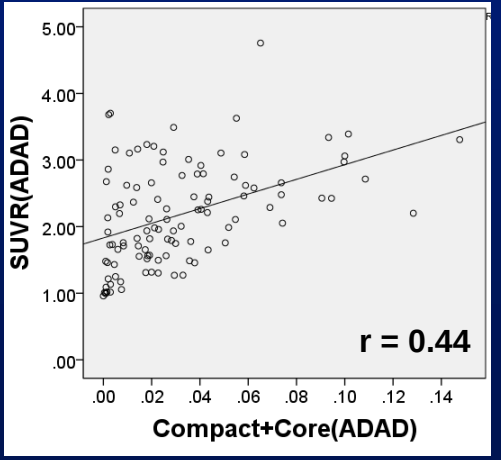




ADAD







Aihong Zhou, unpublished

Comorbidities in AD in ADNI and DIAN Participants

Neuropathologic Diagnoses		LOAD (ADNI)		ADAD (DIAN)	
Primary	Comorbidities^	N=33*	%	N=22**	%
AD	None	14	42.4	11	50
AD	DLB/ALB	14	42.4	11†	50
AD	TDP-43	7	21.2	0	0
AD	AGD	6	18.2	0	0
AD	Hippocampal sclerosis	2	6.1	0	0
AD	Infarcts	1	3.0	0	0
AGD	None	1	3.0	0	0

***7 cases pending; **2 cases pending; ^more than one comorbidity may be present in a single case; †, one case had additional glioblastoma multiforme.**

- Average age at death = 80.7y (ADNI) and 52.4y (DIAN)

<Confidential>

Nigel Cairns, unpublished

Preliminary Conclusions Re: ADAD Pathogenesis – I.

- Elevated $A\beta_{42}$ levels in MCs :
  - In plasma over course of disease, c/w $A\beta_{42}$ overexpression
  - In CSF initially, then reduced in aSx phase -25 to -15y from EYO
- Elevated CSF tau/ptau in aSx MCs -20 to -15y from EYO
- Longitudinal decreases in CSF tau/ptau in symptomatic AD (DIAN and ADNI samples): suggest greatest period of neuronal injury/death is in aSx phase?

Preliminary Conclusions Re: ADAD Pathogenesis – II.

- Baseline amyloid imaging and CSF tau in aSx MCs predict future cognitive decline
- PIB correlates with diffuse and cored plaques
- Synucleinopathy frequent in pure AD; other AD comorbidities (eg, TDP-43; hipp sclerosis) may reflect age?

Other Secondary Prevention Trials

- Alzheimer Prevention Initiative; E Reiman, P Tariot
  - *PSEN1* E280A family; conducted in Colombia
    - 200 MC and 100 NC; began in late 2013
    - Crenezumab (Genentech), subcutaneous
  - *APOE4* homozygotes
    - In Europe and North America, 1300 cognitively healthy people between 60 and 75 years old; to begin in 2015
    - Two arms: Aβ vaccine and beta-secretase inhibitor (Novartis)
- A4 (Anti-Amyloid in Asymptomatic AD); R Sperling, ADCS
  - In North America, clinically normal persons 65-85 y with elevated brain amyloid (PIB), 500 individuals per treatment arm
  - Solanezumab (Eli Lilly), IV infusion every 4 wks for 3 y
- TOMMORROW; Takeda and Zinfandel Pharmaceuticals
  - 5800 cognitively normal persons at increased AD risk based on *APOE* and *TOMM40* genotypes, age 65-83 y worldwide
  - Pioglitazone (AD-4833, PPAR-γ), oral

Through public/private support and partnership, the DIAN-TU has launched trials to provide advancement of treatments, scientific understanding, and improvements in the approach to Alzheimer disease drug developments.

alzheimer's association®

DIAN Pharma Consortium

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DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit

NATIONAL INSTITUTE ON AGING
National Institutes of Health

U01 AG042791
R01 AG046179-01
U01 AG042791-02S

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GHR foundation®

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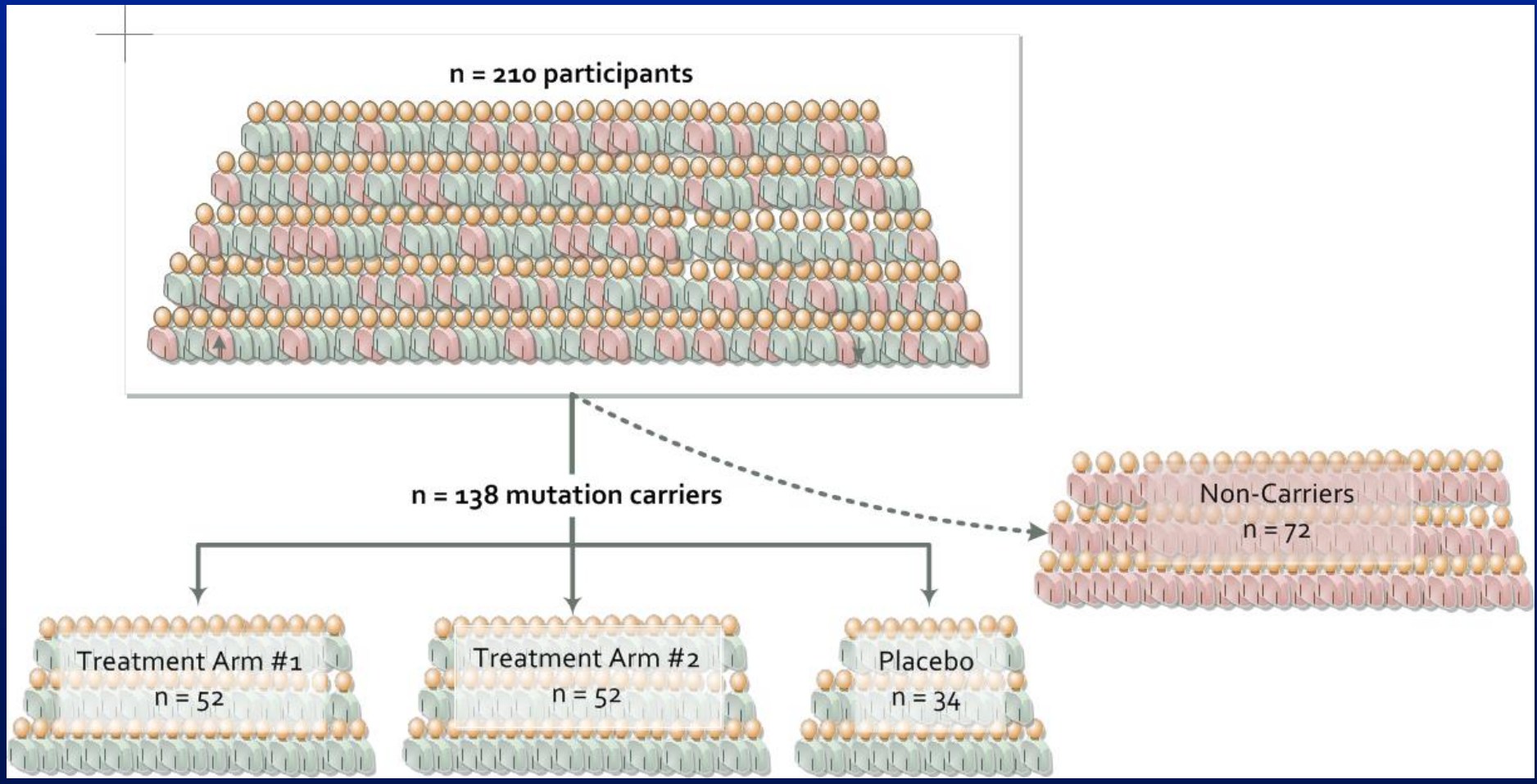
First Drugs in the DIAN Trial

DRUG	TYPE	BM OUTCOME (TARGET)	BM OUTCOME (DOWNSTREAM)
Solanezumab (LILLY)	Anti-Aβ antibody (soluble Aβ)	CSF Aβ40, Aβ42	CSF tau, ptau181, PET PIB, vMRI
Gantenerumab (ROCHE)	Anti-Aβ antibody (fibrillar Aβ)	PET PIB	CSF Aβ40, Aβ42, tau, ptau181, vMRI

2 y BM outcome, then 3 y cognitive outcome for most promising drug(s)

DIAN-TU Trial Design

Biomarker Phase for parallel adaptive drug design. Enrollment of both mutation carriers and non-carriers. Option of non-disclosure of genetic status to participate in the DIAN-TU trial.



DIAN-TU Trial Status

- Present
  - 10 US, 3 Australian , 5 French, 3 Canadian, 1 UK, and 1 Spain site actively recruiting; 4 pending activation (2 US, 2 int'l)
  - 100 participants consented, 25 in screen
  - 64 participants randomized and dosed – 11 screen fail, 1 early termination
- Future: 2 international sites will be active
  - Italy (2 sites) – Mar/Apr
- DIAN: www.dian-info.org; DIAN Expanded Registry: www.DIANexr.org (or 844-342-6297)